

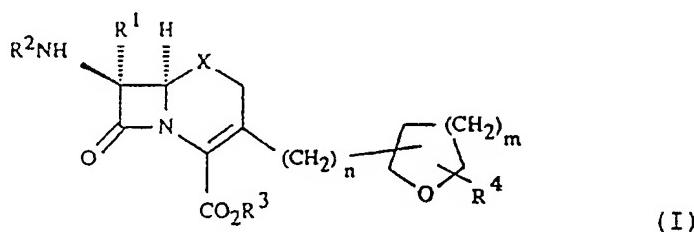


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(54) Title: CEPHALOSPORINS AND HOMOLOGUES, PREPARATIONS AND PHARMACEUTICAL COMPOSITIONS



(57) Abstract

Compounds of formula (I) or a salt thereof, processes for their preparation, their use as antibiotics, and intermediates thereto, wherein R¹ is hydrogen, methoxy or formamido; R² is an acyl group, in particular that of an antibacterially active cephalosporin; CO₂R³ is a carboxy group or a carboxylate anion, or R³ is a readily removable carboxy protecting group; R⁴ represents up to four substituents which may be the same or different; m is 1 or 2; and n is 1.

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CEPHALOSPORINS AND HOMOLOGUES, PREPARATIONS AND PHARMACEUTICAL COMPOSITIONS.

This invention relates to novel β -lactam containing compounds, their preparation and their use, and in particular to a novel class of cephalosporins. These compounds have antibacterial properties, and are therefore of use in the treatment of bacterial infections in humans and animals caused by a wide range of organisms.

10 GB 1 405 758 (Beecham Group Ltd) discloses the compound 3-(2-tetrahydropyranylmethyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid and records its in vitro activity (MIC) against five typical Gram-positive bacteria.

Intermediates thereto in the form of the
15 α -butyl-4-carboxylate and the corresponding 7-amino-and 7-triphenylmethylamino- α -butyl esters are also disclosed.

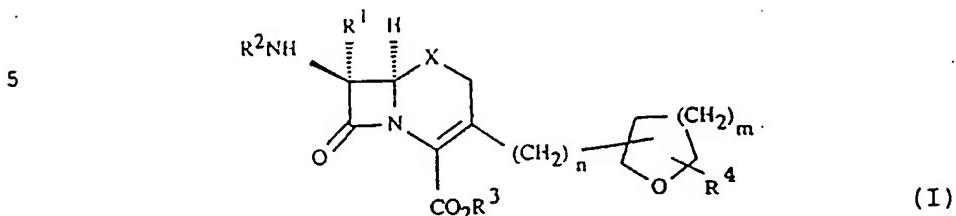
Nayler J.H.C. et al. (Journal of Medicinal Chemistry, 1977, Vol 20,) discloses the compound 3-(2-tetrahydropyranyl-
20 methyl)-7 β -(D- α -phenylglycyl)aminoceph-3-em-4-carboxylic acid and records its in vitro activity (MIC) against two Gram-positive and five Gram-negative bacteria.

Intermediates thereto in the form of the 7-amino- and
25 7 β -(N- α -butoxycarbonyl-D- α -phenylglycyl)amino-
 α -butyl-4-carboxylate derivatives are also disclosed.

We have now found a particular class of cephalosporins bearing a cyclic ether substituent at the 3-position of the cephalosporin nucleus that possesses prolonged and high
30 levels of antibacterial activity, and shows good absorption both parentally and orally, especially orally.

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The present invention provides a compound of formula (I) or a salt thereof:



10 wherein

R¹ is hydrogen, methoxy or formamido;
 R² is an acyl group, in particular that of an
 antibacterially active cephalosporin;
 CO₂R³ is a carboxy group or a carboxylate anion, or R³ is a
 15 readily removable carboxy protecting group (such as a
 pharmaceutically acceptable in-vivo hydrolysable ester
 group); R⁴ represents up to four substituents selected
 from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen,
 amino, alkylamino, acylamino, dialkylamino, CO₂R, CONR₂,
 20 SO₂NR₂ (where R is hydrogen or C₁₋₆ alkyl), aryl and
 heterocyclyl, which may be the same or different and
 wherein any R⁴ alkyl substituent is optionally substituted
 by any other R⁴ substituent; X is S, SO, SO₂, O or CH₂; m is 1
 or 2; and n is 1, subject to the proviso that when R¹ is
 25 hydrogen, X is S and the 3-position substituent is
 unsubstituted tetrahydropyran-2-ylmethyl (m=2), then, when
 R³ is hydrogen, R² is not 2-thienylacetyl or
 D-α-aminophenylacetyl, and when R³ is t-butyl, R² is not
 2-thienylacetyl, D-α-aminophenylacetyl or
 30 N-t-butoxycarbonyl-D-α-amino-phenylacetyl.

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The bonding carbon atom of the cyclic ether moiety which links the ring to the cephalosporin nucleus is generally asymmetric. The present invention includes either stereoisomer, as well as mixtures of both isomers.

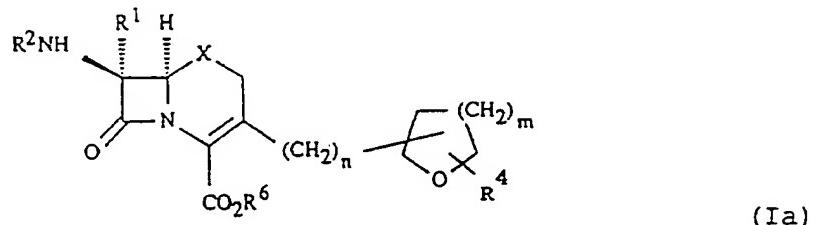
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In compounds of formula (I) wherein R¹ is formamido, the formamido group can exist in conformations wherein the hydrogen atoms of the -NH-CHO moiety are cis- or trans-; of these the cis conformation normally predominates.

10

Since the β -lactam antibiotic compounds of the present invention are intended for use as therapeutic agents in pharmaceutical compositions, it will be readily appreciated that preferred compounds within formula (I) are 15 pharmaceutically acceptable, i.e. are compounds of formula (Ia) or pharmaceutically acceptable salts or pharmaceutically acceptable in vivo hydrolysable esters thereof:

20



25

wherein R¹, R², R⁴, m, n and X are as defined with respect to formula (I) and the group CO₂R⁶ is CO₂R³ where CO₂R³ is a carboxy group or a carboxylate anion.

30 Accordingly, the present invention provides a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use as a therapeutic agent, and in particular an in vivo hydrolysable ester

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thereof for use as an orally administrable therapeutic agent.

The present invention further provides a compound of formula 5 (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the treatment of bacterial infections, more particularly an in vivo hydrolysable ester thereof for use in the oral treatment of bacterial infections.

10

The present invention also includes a method of treating bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of an antibiotic compound of this invention of the formula (Ia) 15 or a pharmaceutically acceptable in vivo hydrolysable ester thereof, in particular the oral administration of a therapeutically effective amount of an in vivo hydrolysable ester.

20 In addition, the present invention includes the use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for the manufacture of a medicament for the treatment of bacterial infections, in particular the use of an in vivo hydrolysable 25 ester for the manufacture of a medicament for the oral treatment of bacterial infections.

Those compounds of the formula (I) wherein R³ is a readily removable carboxy protecting group other than a 30 pharmaceutically acceptable in vivo hydrolysable ester or which are in non-pharmaceutically acceptable salt form are primarily useful as intermediates in the preparation of compounds of the formula (Ia) or a pharmaceutically acceptable salt or pharmaceutically acceptable in vivo 35 hydrolysable ester thereof.

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Suitable readily removable carboxy protecting groups for the group R³ include groups forming ester derivatives of the carboxylic acid, including in vivo hydrolysable esters. The derivative is preferably one which may readily be cleaved in vivo.

It will be appreciated that also included within the scope of the invention are salts and carboxy-protected derivatives, including in vivo hydrolysable esters, of any carboxy groups that may be present as optional substituents in compounds of formula (I) or (Ia). Also included within the scope of the invention are acid addition salts of any amino group or substituted amino group that may be present as optional substituents in compounds of formula (I) or (Ia).

Suitable ester-forming carboxyl-protecting groups are those which may be removed under conventional conditions. Such groups for R³ include benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula -N=CHR⁷ where R⁷ is aryl or heterocyclic, or an in vivo hydrolysable ester radical such as defined below.

When used herein the term 'aryl' includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, C₁₋₆ alkyl, phenyl, C₁₋₆ alkoxy, hydroxy(C₁₋₆)alkyl, mercapto(C₁₋₆)alkyl, halo(C₁₋₆) alkyl, hydroxy, amino, nitro, carboxy, C₁₋₆ alkylcarbonyloxy, alkoxycarbonyl, formyl, or C₁₋₆ alkylcarbonyl groups.

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The terms 'heterocyclyl' and 'heterocyclic' as used herein include aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may 5 be unsubstituted or substituted by, for example, up to three groups selected from halogen, (C₁₋₆)alkyl, (C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, aryl, and oxo groups. Each 10 heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. The term 'heteroaryl' refers to heteroaromatic heterocyclic rings. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention 15 containing a heterocyclyl group may occur in two or more tautomeric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

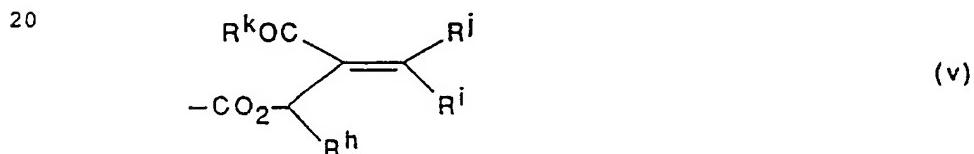
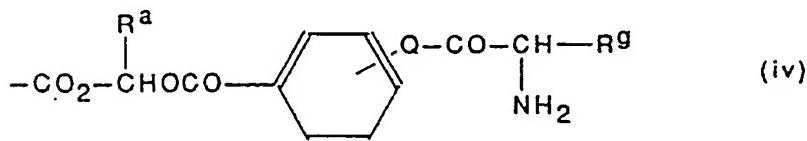
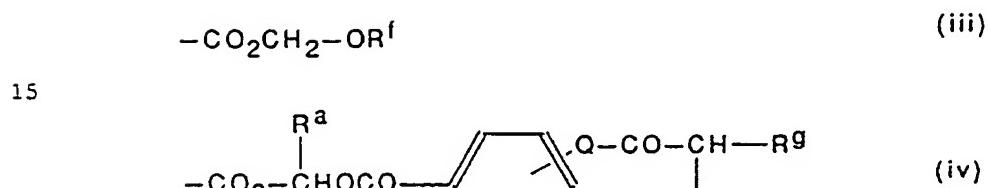
When used herein the terms 'alkyl' alkenyl, alkynyl and 'alkoxy' include straight and branched chain groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl. A particular alkyl group is methyl.

25 When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine.

A carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R³ 30 group, for example, acid- and base- catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenolysis under conditions wherein the remainder of the molecule is substantially unaffected.

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Examples of suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of 5 part formulae (i), (ii), (iii), (iv) and (v):



wherein R^a is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, methyl, 25 or phenyl, R^b is C₁₋₆ alkyl, C₁₋₆ alkoxy, phenyl, benzyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyloxy, C₁₋₆ alkyl C₃₋₇ cycloalkyl, 1-amino C₁₋₆ alkyl, or 1-(C₁₋₆ alkyl)amino C₁₋₆ alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c 30 represents C₁₋₆ alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent C₁₋₆ alkyl; R^f represents C₁₋₆ alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, C₁₋₆ alkyl, or C₁₋₆ alkoxy; Q is 35 oxygen or NH; R^h is hydrogen or C₁₋₆ alkyl; Rⁱ is hydrogen, C₁₋₆ alkyl optionally substituted by halogen, C₂₋₆ alkenyl,

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C_{1-6} alkoxy carbonyl, aryl or heteroaryl; or R^h and R^i together form C_{1-6} alkylene; R^j represents hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy carbonyl; and R^k represents C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-6} alkoxy(C_{1-6}) alkoxy or aryl.

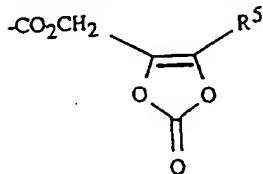
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Examples of suitable in vivo hydrolysable ester groups include, for example, acyloxyalkyl groups such as acetoxy methyl, pivaloyloxymethyl, α -acetoxyethyl, α -pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; alkoxy carbonyloxyalkyl groups, such as ethoxycarbonyloxy methyl, α -ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; dialkylaminoalkyl especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, 15 dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl; and esters linked to a second β -lactam antibiotic or to a β -lactamase inhibitor.

A preferred in vivo hydrolysable ester group is the pivaloyloxymethyl ester.

25 A further suitable pharmaceutically acceptable in vivo hydrolysable ester group is that of the formula:

30



wherein R^5 is hydrogen, C_{1-6} alkyl or phenyl.

Suitable pharmaceutically acceptable salts of the carboxy group of the compound of formula (I) include metal salts, eg 35 aluminium, alkali metal salts such as sodium or potassium,

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especially sodium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 5 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)- amine, cycloalkylamines such as dicyclohexylamine, or with procaine, dibenzylamine, N,N-dibenzylethylene- diamine, 1-ephedamine, N-methylmorpholine, N-ethyldipiperidine, 10 N-benzyl- β -phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, ethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins and cephalosporins. Other useful salts 15 include the lithium salt and silver salt. Salts within compounds of formula (I), may be prepared by salt exchange in conventional manner.

In compounds of formula (I) or (Ia), the group X may be 20 sulphur or an oxidised sulphur atom, i.e. a sulphoxide (SO) or sulphone (SO₂) group. When X is a sulphoxide group it will be understood that α - and β -isomers may exist; both such isomers are encompassed within the scope of the present invention.

25 Preferably X is sulphur.

Advantageously, R¹ is hydrogen.

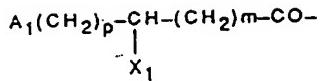
Suitably, the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted or substituted by up 30 to three substituents, R⁴, selected from C₁₋₆ alkyl, C₁₋₆ alkoxy C₁₋₆ alkoxy carbonyl C₁₋₆ alkoxy C₁₋₆ alkyl, and C₁₋₆ alkanoyloxy C₁₋₆ alkyl. Preferably the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted. Preferably m is 1.

35 Preferably the cyclic ether is bonded to the cephalosporin nucleus at a ring carbon adjacent to the oxygen heteroatom.

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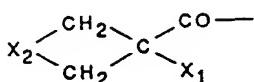
Suitable acyl groups R² include those of formulae (a) - (f):

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(a)

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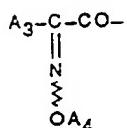
(b)

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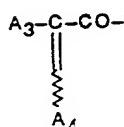


(d)

20



(e)



(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A₁ is C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₆ cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic (including heteroaromatic) group, such as phenyl, substituted phenyl, thiophenyl, pyridyl, or an optionally substituted thiazolyl group, a C₁₋₆ alkylthio group or C₁₋₆ alkyloxy; X₁ is a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group;

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A₂ is an aromatic group, for example a phenyl, 2,6-dimethoxyphenyl, 2-alkoxy-1-naphthyl, 3-arylisoxazolyl, or a 3-aryl-5-methylisoxazolyl group, such as 3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl; 5 a substituted alkyl group; or a substituted dithietane; X₂ is a -CH₂OCH₂-, -CH₂SCH₂- or alkylene group; X₃ is an oxygen or sulphur atom; A₃ is an aryl or heteroaryl group such as phenyl, substituted phenyl, furyl, aminothiazolyl or aminothiadiazolyl in which the amino group is optionally 10 protected; and A₄ is hydrogen, C₁₋₆alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl(C₁₋₆)alkyl, C₁₋₆ alkoxy carbonyl(C₁₋₆) alkyl, C₂₋₆ alkenyl, carboxy(C₁₋₆)alkyl, C₂₋₆ alkynyl, aryl or C₁₋₆alkyl substituted by up to three aryl groups.

15 The term 'heteroaryl' as used herein means a heteroaromatic heterocyclic ring or ring system, suitably having 5 or 6 ring atoms in each ring.

Suitably when R² is a group (a), A₁ is C₁₋₆ alkyl, C₃₋₆ 20 cycloalkyl, cyclohexenyl, cyclohexadienyl, phenyl, substituted phenyl such as hydroxyphenyl, thienyl or pyridyl; and X₁ is a hydrogen or halogen atom, or a carboxy, carboxylic ester, azido, tetrazolyl, hydroxy, acyloxy, optionally protected amino, ureido, guanidino or acylureido 25 group.

Suitably when R² is a group of formula (d), A₂ is phenyl, X₃ is oxygen and p is 0.

30 Alternatively when R² is a group of formula (e) or (f) suitable values for the group A₃ include those commonly found in antibacterially active cephalosporins containing a hydroxyimino, substituted hydroxyimino or vinyl group in the side chain attached to position 7 of the cephalosporin 35 nucleus, for example phenyl, thien-2-yl, thien-3-yl,

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fur-2-yl, fur-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl,
5-amino-1,2,4-thiadiazol-3-yl and 2-aminothiazol-4-yl in
each of which the amino group is optionally protected.

5 Preferred groups for A₃ include phenyl, 2-aminothiazol-4-yl,
fur-2-yl, thien-2-yl, 2-(2-chloroacetamido)thiazol-4-yl,
2-tritylamino-thiazol-4-yl, 5-amino-1,2,4-thiadiazol-3-yl
and 4-aminopyrimid-2-yl.

10 In compounds of formula (Ia), a particularly preferred group
for A₃ is 2-aminothiazol-4-yl.

Suitable values for the group A₄ include hydrogen, methyl,
ethyl, cyclopropylmethyl, triphenylmethyl (trityl),
15 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
cyclooctyl, phenyl, carboxymethyl, carboxypropyl and
t-butoxycarbonylmethyl.

Preferred values for A₄ in compounds of formula (Ia) include
20 methyl and hydrogen.

It will be appreciated that compounds of the invention
wherein R² is a group of formula (e) (or (f)) can exist as
syn and anti (or E and Z) isomers or mixtures thereof. Both
25 isomers are encompassed within the scope of this invention.

Preferably the compounds of the invention wherein R² is a
group of formula (e) have the syn configuration (i.e. have
the group OA₄ syn to the amide linkage) or are enriched in
30 that isomer.

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Similarly, when R² is a group of formula (f), the group A₄ is preferably cis to the amide linkage, i.e. when group (f) is 2-amino-thiazol-4-yl, the Z-configuration is preferred.

5 Certain compounds of the invention include an amino group which may be protected. Suitable amino protecting groups are those well known in the art which may be removed under conventional conditions without disruption of the remainder of the molecule.

10

Examples of amino protecting groups include C₁₋₆ alkanoyl; benzoyl; benzyl optionally substituted in the phenyl ring by one or two substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethyl, halogen, or nitro; C₁₋₄ 15 alkoxy carbonyl; benzyloxycarbonyl or trityl substituted as for benzyl above; allyloxycarbonyl, trichloroethoxycarbonyl or chloroacetyl.

Some of the compounds of this invention may be crystallised 20 or recrystallised from solvents such as organic solvents.

In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as 25 lyophilisation.

Since the antibiotic compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure 30 form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 95% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; 35 these less pure preparations of the compounds should contain

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at least 1%, more suitably at least 5% and preferably from 10 to 49% of a compound of the formula (I) or salt thereof.

Specific compounds within this invention of formula (Ia) include the following pharmaceutically acceptable carboxylic acids, salts and in-vivo hydrolysable esters:

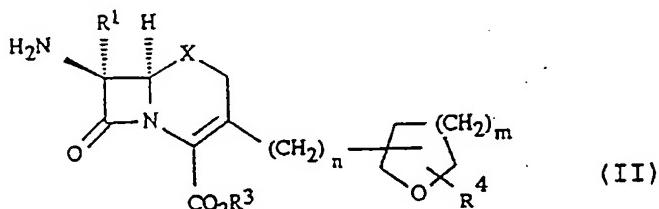
sodium (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate; and

pivaloyloxymethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate.

15

The present invention further provides a process for the preparation of a compound of formula (I), which process comprises treating a compound of formula (II) or a salt thereof:

20



25

wherein R¹, CO₂R³, R⁴, m, n and X are as hereinbefore defined, wherein any reactive groups may be protected, and wherein the amino group is optionally substituted with a 30 group which permits acylation to take place; with an N-acylating derivative of an acid of formula (III):

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wherein R^2 is as defined with respect to formula (I) and
5 wherein any reactive groups may be protected; and
thereafter, if necessary or desired, carrying out one or
more of the following steps:

- i) removing any protecting groups;
- 10 ii) converting the group CO_2R^3 into a different group $\text{CO}_2\text{R}'^3$;
- 15 iii) converting the group R^2 into a different group R'^2 ;
- iv) converting the group X into a different group X';
- v) converting the product into a salt.

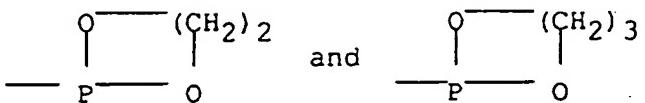
20 Acids of formula (III) may be prepared by methods known in the art, or methods analogous to such processes. Suitable processes include those described, for example, in UK Patent 2 107 307 B, UK Patent Specification No. 1,536,281, and U.K. 25 Patent Specification No. 1,508,064.

Suitable groups which permit acylation to take place and
which are optionally present on the amino group of the
starting material of the formula (II) include N-silyl,
30 N-stannyl and N-phosphorus groups, for example trialkylsilyl
groups such as trimethylsilyl, trialkyltin groups such as
tri-n-butyltin, groups of formula $-\text{P.R}^{20}\text{R}^{21}$ wherein R^{20} is
an alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkyl, aryl,
aralkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy or

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dialkylamino group, R²¹ is the same as R²⁰ or is halogen or R²⁰ and R²¹ together form a ring; suitable such phosphorus groups being -P(OC₂H₅)₂, -P(C₂H₅)₂,

5



A group which may optionally be introduced onto the amino 10 group in the compound of formula (II) is trimethylsilyl.

Advantageously the silylation reaction may be carried out in situ, prior to the acylation reaction, with a silylating agent that does not require concomitant addition of base.

15 Suitable silylating agents include, for example,

N-(trimethylsilyl)-acetamide,

N,O-bis-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)-trifluoroacetamide, N-methyl-N-trimethylsilylacetamide,

N-methyl-N-trimethylsilyl-trifluoroacetamide,

20 N,N'-bis(trimethylsilyl)urea, and

N,O-bis(trimethylsilyl)carbamate. A preferred silylating agent is N,O-bis(trimethylsilyl)acetamide. The silylation reaction may suitably be carried out in an inert, anhydrous organic solvent such as dichloromethane at room temperature 25 or at an elevated temperature, for example 30 - 60°C, preferably 40 - 50°C.

The above process may optionally be carried out in the presence of a small quantity, for example 0.1 equivalents, 30 of a silyl halide, for example a tri(C₁₋₆)alkylsilyl halide, especially trimethylsilyl chloride.

A reactive N-acylating derivative of the acid (III) is employed in the above process. The choice of reactive

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derivative will of course be influenced by the chemical nature of the substituents of the acid.

Suitable N-acylating derivatives include an acid halide, 5 preferably the acid chloride or bromide or alternatively a symmetrical or mixed anhydride. The acylation may be effected in the presence of an acid binding agent for example, tertiary amine (such as pyridine or dimethylaniline), molecular sieves, an inorganic base (such 10 as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{1-6})-1,2-alkylene oxide - such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out 15 at a temperature in the range -50°C to $+50^{\circ}\text{C}$, preferably -20°C to $+20^{\circ}\text{C}$, in aqueous or non-aqueous media such as water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. 20 Alternatively, the reaction may be carried out in an unstable emulsion of water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate. The acylation with acid halide or anhydride is suitably carried out in the presence of a basic catalyst 25 such as pyridine or 2,6-lutidine.

Acid halides may be prepared by reacting the acid (III) or a salt or a reactive derivative thereof with a halogenating (eg chlorinating or brominating) agent such as phosphorus 30 pentachloride, thionyl chloride, oxalyl chloride or phosgene.

Suitable mixed anhydrides are anhydrides with, for example, carbonic acid monoesters, trimethyl acetic acid, thioacetic 35 acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric, phosphorous, and phosphinic acids) or

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aromatic or aliphatic sulphonic acids (such as p-toluenesulphonic acid or methanesulphonic acid).

Alternative N-acylating derivatives of acid (III) are the
5 acid azide, or activated esters such as esters with
2-mercaptopuridine, cyanomethanol, p-nitrophenol,
2,4-dinitrophenol, thiophenol, halophenols, including
pentachlorophenol, monomethoxyphenol, N-hydroxy succinimide,
N-hydroxybenzotriazole, or 8-hydroxyquinoline; or amides
10 such as N-acylsaccharins, N-acylthiazolidin-2-thione or
N-acylphtalimides; or an alkylidene iminoester prepared by
reaction of the acid (III) with an oxime.

Other reactive N-acylating derivatives of the acid (III)
15 include the reactive intermediates formed by reaction in
situ with a condensing agent such as a carbodiimide, for
example, N,N'-diethyl-, dipropyl- or
diisopropylcarbodiimide, N,N'-di-cyclohexyl-carbodiimide, or
N-ethyl-N'-[3-(dimethylamino)propyl]- carbodiimide; a
20 suitable carbonyl compound, for example,
N,N'-carbonyldiimidazole or N,N'-carbonyldi- triazole; an
isoxazolinium salt, for example,
N-ethyl-5-phenyloxazolinium-3-sulphonate or N-t-butyl-5-
methylloxazolinium perchlorate; or an N-alkoxycarbonyl
25 2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl
2-ethoxy-1,2-dihydroquinoline. Other condensing agents
include Lewis acids (for example $BBr_3 - C_6H_6$);
or a phosphoric acid condensing agent such as
diethylphosphorylcyanide. The condensation reaction is
30 preferably carried out in an organic reaction medium, for
example, methylene chloride, dimethylformamide,
acetonitrile, alcohol, benzene, dioxan or tetrahydrofuran.

A further method of forming the N-acylating derivative of
35 the acid of formula (III) is to treat the acid of formula
(III) with a solution or suspension preformed by addition of

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a carbonyl halide, preferably oxalyl chloride, or a phosphoryl halide such as phosphorus oxychloride, to a halogenated hydrocarbon solvent, preferably dichloromethane, containing a lower acyl tertiary amide, preferably 5 N,N-dimethylformamide. The N-acylating derivative of the acid of formula (III) so derived may then be caused to react with a compound of formula (II). The acylation reaction may conveniently be carried out at -40° to +30°C, if desired in the presence of an acid binding agent such as pyridine. A 10 catalyst such as 4-dimethylaminopyridine may optionally also be added. A preferred solvent for the above acylation reaction is dichloromethane.

The optional reduction step, the optional conversion of R² 15 to a different R², CO₂R³ to a different CO₂R³ and X to a different X, and the optional formation of a salt, may be carried out using methods well known in the art of cephalosporin and penicillin chemistry.

20 For example, when the group X is S, SO, or SO₂, the group X may be converted into a different group X by methods of oxidation or reduction well known in the art of cephalosporin and penicillin synthesis, as described, for example, in European Patent Application Publication No. 0 25 114 752. For example, sulphoxides (in which X is SO) may be prepared from the corresponding sulphide (in which X is S) by oxidation with a suitable oxidising agent, for example an organic peracid such as m-chloroperbenzoic acid.

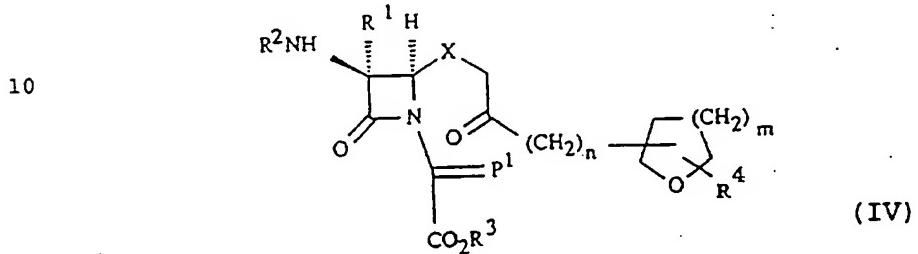
30 A reduction step is generally effected by processes well known in the art of β-lactam chemistry, for example using phosphorus trichloride in dimethylformamide.

In the process described hereinabove, and in the process 35 described hereinbelow, it may be necessary to remove protecting groups. Deprotection may be carried out by any

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convenient method known in the art such that unwanted side reactions are minimised. Separation of unwanted by-products may be carried out using standard methods.

5 In a further process of the invention, compounds of formula (I) may be prepared by cyclising a compound of formula (IV):



15 wherein X, R¹, R², R⁴, m, n and CO₂R³ are as hereinbefore defined and P' is a phosphorus residue; and thereafter if necessary or desired, carrying out one or more of the following steps:

- 20
- i) removing any protecting groups;
 - ii) converting the group CO₂R³ into a different group CO₂R'³;
- 25
- iii) converting the group R² into a different group R'²;
 - iv) converting the group X into a different group X';
- 30 v) converting the product into a salt.

The cyclisation reaction is an intramolecular Wittig-type reaction and is typically carried out by heating the compound of formula (IV) in an organic solvent system, for

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example in toluene, optionally in the presence of a suitable acid such as benzoic acid.

The phosphorus residue, P' is typically a
 5 trialkylphosphoranylidene residue, for example a C₁₋₆
 trialkylphosphoranylidene residue such as
 tri-*n*-butylphosphoranylidene, or a triarylphosphoranylidene
 residue such as triphenylphosphoranylidene.

10 Where R² in a compound of formula (I) is required to be different from the group R² in the compound of formula (IV), the conversion may be effected via the intermediacy of a compound of formula (II) which has an amino group at the 7-position of the cephalosporin nucleus.

15

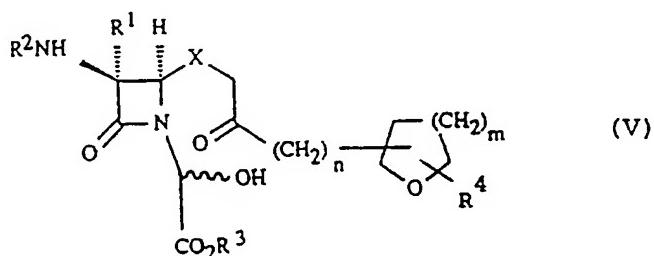
An R² side-chain may be removed by the Delft procedure commonly used in β -lactam chemistry. Suitable reaction conditions include treatment with phosphorus pentachloride and *N*-methylmorpholine at reduced temperature.

20

Compounds of formula (II) are novel compounds and as such form part of the invention.

A compound of formula (IV) may be prepared from a compound
 25 of formula (V) :

30

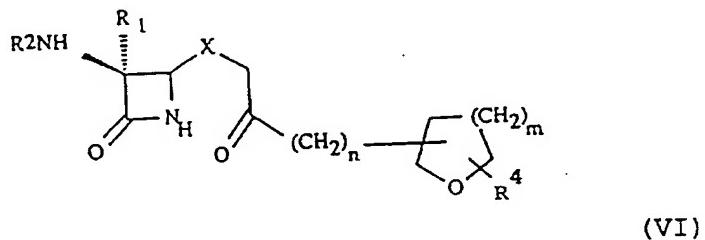


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wherein X, R¹, R², R⁴, m, n and CO₂R³ are as hereinbefore defined, by reaction with a halogenating agent, suitably a chlorinating agent such as thionyl chloride, which reaction displaces the formula (V) hydroxyl group by halogen, 5 suitably chloride, and is typically carried out at reduced temperature in an inert solvent, for example in tetrahydrofuran, in the presence of a base, typically a pyridine derivative such as 2,6-lutidine. Formation of the phosphorane may be effected by treatment of the 10 halo-intermediate with an appropriate phosphine derivative, for example tri-n-butylphosphine or triphenylphosphine, suitably at ambient temperature in an inert solvent such as dioxan.

15 A compound of formula (V) may be prepared by reaction of a compound of formula (VI):

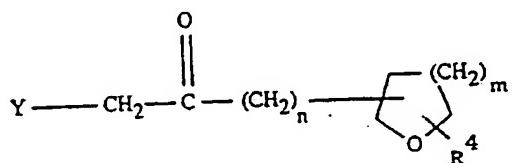
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25 wherein X, R¹, R², R⁴, m and n are as hereinbefore defined with an ester of glyoxylic acid (OCHCO₂R³) in the presence of triethylamine.

In a typical preparation of a compound of formula (VI) in 30 which X is sulphur, a compound of formula (VII):

(VII)



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wherein Y is a leaving group and R⁴, m and n are as hereinbefore defined is reacted with a compound of formula (VIII) :

5

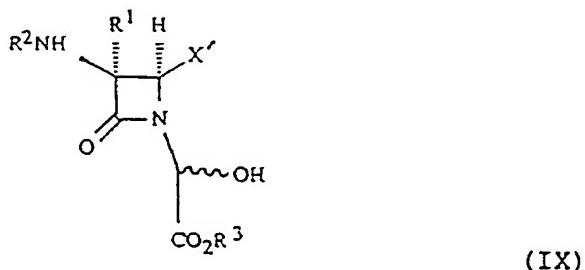


wherein R¹ and R² are as hereinbefore defined.

10 Suitably, a leaving group Y is halogen, for example chloro. The reaction may be carried out at ambient temperature in an inert solvent, for example acetone or dimethylformamide, in the presence for a base, for example potassium carbonate.

15 A compound of formula (V) may also be prepared by reaction of a compound of formula (IX) :

20



25 wherein R¹, R² and CO₂R³ are as hereinbefore defined and X' is an X-group precursor, with a compound of formula (VII) as hereinbefore defined.

In a typical preparation of a compound of formula (V) in
30 which X is sulphur, a Y leaving group in a compound of formula (VII), suitably a halogen such as chloro or bromo, is displaced by an X' mercapto group in a compound of formula (IX). The reaction may be carried out at ambient

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temperature in an inert solvent, for example acetone, with the addition of base, for example potassium carbonate, before work-up.

5 Azetidin-2-one compounds of formulae (VIII) and (IX) may be prepared according to known methods in heterocyclic synthetic chemistry and particularly by known methods in the art of β -lactam chemistry. For example a compound of formula (VIII) may be prepared according to the method of 10 Osborne N.F. et al., J. Chem. Soc., Perkin Trans. I, 146, 1980.

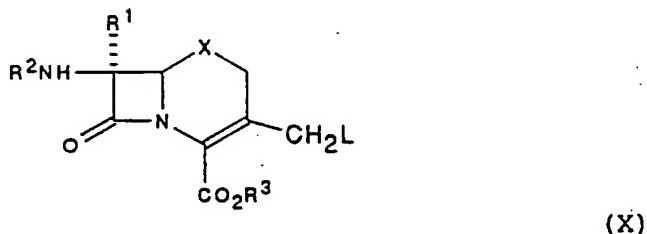
A compound of formula (IX) in which X' is a mercapto group may be prepared by ring opening of a 4-thia-2,6-diazabicyclo 15 [3.2.0]-hept-2-ene-7-one derivative according to the method of Masayuki Narisada et al., Tetrahedron Lett., 1755 (1978).

Compounds of formula (VII) are known compounds or may be prepared by standard methodology. For example, the 20 compounds of formula (VII) in which Y is chloro or bromo may be prepared from the corresponding carboxylic acid (Y=COOH) via formation of the acid chloride followed by treatment with diazomethane and reaction of the resulting diazo compound with hydrogen chloride or hydrogen bromide.

25

In a further process of the invention, compounds of formula (I) may be prepared directly by organo-cuprate displacement of a leaving group at the 3-position of a compound of formula (X):

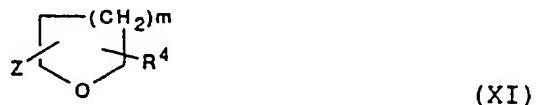
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35

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wherein R¹, R², CO₂R³ and X are as hereinbefore defined and L is a leaving group, suitably a halogen, mesylate, triflate or fluorosulphonate leaving group, by reaction with a compound of formula (XI):



10

wherein Z is an organo-cuprate group and R⁴ and m are as hereinbefore defined.

A compound with a halogen 3-position leaving group, for example chloro, in which X is sulphur may be prepared by the procedure of Fujumoto K. et al., J. Antibiotics, 40, 370, (1987).

A compound with a 3-position leaving group, L, in which X is CH₂ may be prepared from the hydroxy intermediate, prepared as described by S. Uyeo and H. Ona, Chem. Pharm. Bull., 28, 1563, (1980).

It should be noted that in processes of this invention 25 Δ²-cephems may function as intermediates, in the synthetic sequences. Subsequent isomerisation steps by methods well known in cephalosporin chemistry will provide the Δ³-cephems of the invention.

30 The present invention also provides a pharmaceutical composition which comprises a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

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The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

5

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

10

The composition may be formulated for administration by any route, such as oral, topical or parenteral, especially oral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, 15 such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings 20 and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional 25 carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

30 Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, 35 maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc,

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polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

20

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed

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under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use.

PARENTERAL suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration.

Such a dosage corresponds to 1.5 to 50 mg/kg per day.

Suitably the dosage is from 5 to 20 mg/kg per day.

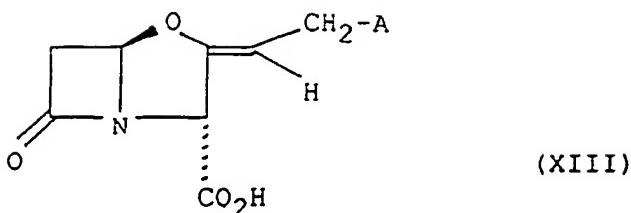
No unacceptable toxicological effects are expected when a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (Ia) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β -lactamase inhibitor may be employed.

Advantageously, the compositions also comprise a compound of formula (XIII) or a pharmaceutically acceptable salt or ester thereof:

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5



(XIII)

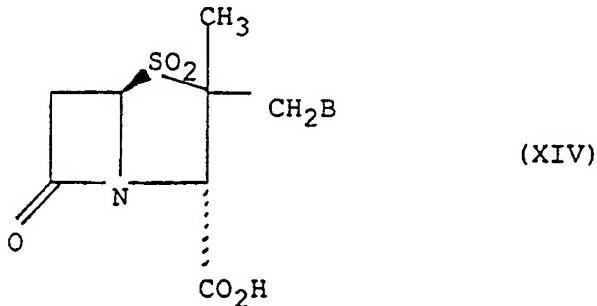
wherein

10 A is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl- substituted amino, or mono- or di-acylamino; an optionally substituted triazolyl group; or an optionally substituted tetrazolyl group as described in EP-A-0 053 893.

15

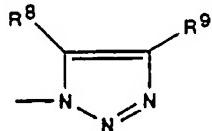
A further advantageous composition comprises a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof together with a compound of formula (XIV) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof:

25



30 wherein

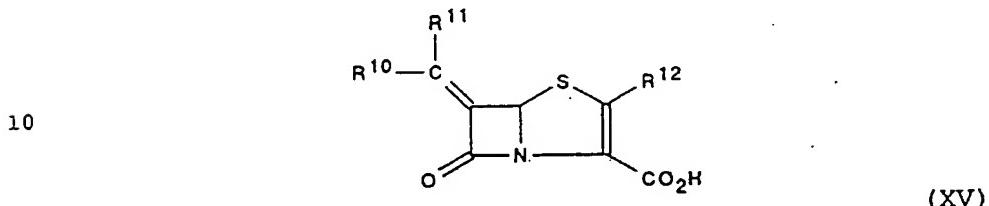
B represents hydrogen, halogen or a group of formula:



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in which R⁸ and R⁹ are the same or different and each represents hydrogen, C₁₋₆ alkoxy carbonyl or carboxy, or a pharmaceutically acceptable salt thereof.

5 Further suitable β -lactamase inhibitors include 6-alkylidene penems of formula (XV) :



or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, wherein R¹⁰ and R¹¹ are the same or different and each represents hydrogen, or a C₁₋₁₀ hydrocarbon or heterocyclic group optionally substituted with a functional group; and R¹² represents hydrogen or a group of formula R¹³ or -SR¹³ where R¹³ is an optionally substituted C₁₋₁₀ hydrocarbon or heterocyclic group, as described in EP-A-0 041 768.

Further suitable β -lactamase inhibitors include 6 β -bromopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof and 6 β -iodopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof described in, for example, EP-A-0 410 768 and EP-A-0 154 132 (both Beecham Group).

30

Such compositions of this invention which include a β -lactamase inhibitory amount of a β -lactamase inhibitor are formulated in a conventional manner using techniques and procedures per se known in the art.

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The antibiotic compounds of the present invention are active against a wide range of organisms including both Gram-negative organisms such as E.coli and Gram-positive organisms such as S.aureus.

The following Examples illustrate the preparation of compounds of the invention and intermediates thereto. The following biological data illustrate the activity of a compound of the invention in the form of MIC values (minimum inhibitory concentration) against a sample E.coli organism (NCTC 10418) and a sample S.aureus organism (S.aureus Oxford).

15

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Example 1

Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-methoxy-iminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-5-3-em-4-carboxylate

(a) Tetrahydrofuran-2-ylacetic acid

Benzyl tetrahydrofuran-2-ylacetate (0.4g, K.T. Mead and 10 B. Samuel, Tetrahedron Lett., 1988, 29, 6573), in tetrahydrofuran (THF) (10ml) was treated with 10% palladium on carbon catalyst (0.08g) and the mixture hydrogenolysed until there was no further uptake of hydrogen, and t.l.c. analysis showed no starting material. The catalyst was 15 removed by filtration through Kieselguhr. The sufficiently pure title compound was obtained as a colourless, viscous oil on removal of solvent, (0.229g, 97%); ν_{max} (CH_2Cl_2) 3500-2700 (v.br), 1712 cm^{-1} ; δ_{H} (CDCl_3) 1.6-2.4 (4H, m), 2.44-2.89 (2H, m), 3.73-4.12 (2H, m), 4.22-4.51 (1H, m) and 20 11.09 (1H, br.s). [Mass spectrum: +ve ion (NH_3) MH^+ (131) and MNH_4^+ (148)].

(b) 2-(3-Chloro-2-oxoprop-1-yl)tetrahydrofuran

25 Tetrahydrofuran-2-ylacetic acid (4.572g) in dry dichloromethane (50ml) was treated with oxalyl chloride (6.7g, 4.6ml) and then 2-3 drops of dimethylformamide (DMF). After the initial effervescence had subsided the solution was left at ambient temperature for 1.5h. The solvent and 30 excess oxalyl chloride were removed in vacuo and the resultant oil [ν_{max} (CH_2Cl_2) 1797 cm^{-1}] redissolved in dichloromethane (20ml), and added dropwise to an ice bath cooled ethereal solution of diazomethane (ca. 80mmol). T.l.c. analysis (50% ethyl acetate/hexane) showed the diazoketone 35 as a single mobile spot. Hydrogen chloride was bubbled

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through the solution until no more starting material was observed by t.l.c. Silica gel column chromatography afforded the title compound as a pale yellow oil, (1.833g, 32%); (Found: $(M-C_1)^+$, 127.0758. $C_7H_{11}O_2$ requires M, 127.0759); ν_{max} (CH_2Cl_2) 1736cm⁻¹; δ_H ($CDCl_3$) 1.46-1.60 (1H, m), 1.86-1.96 (2H, m), 2.07-2.18 (1H, m), 2.76 (1H, dd, J5.1, 15.6Hz), 2.85 (1H, dd, J7.4, 15.6Hz), 3.74 (1H, dd, J8.2, 15.2Hz), 3.87 (1H, dd, J6.8, 15.2Hz), 4.19 (2H, s) and 4.25 (1H, m).

10

(c) (3R, 4R)-3-Phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-one

(3R, 4R)-4-Mercapto-3-phenoxyacetamidoazetidin-2-one (2.76g) 15 and the chloroketone prepared in Example 1(b), (1.48g) together in DMF (10ml) were treated with potassium carbonate (1.39g) at ambient temperature for about 2h. T.l.c. analysis showed loss of chloroketone. The solution was diluted with ethyl acetate and washed with water (3x) and 20 brine, dried and concentrated. Flash chromatography on silica gel eluting with 80% ethyl acetate in hexane afforded the title compound as a mixture of diastereoisomers as a colourless foam, (2.37g, 60%); [Found: M⁺, 378.1241. $C_{18}H_{22}N_2O_5S$ requires M, 378.1249]; ν_{max} ($CHCl_3$) 3405, 25 3295(br), 1782, 1693 and 1600cm⁻¹; δ_H ($CDCl_3$) 1.49-1.57 (1H, m), 1.84-1.97 (2H, m), 2.02-2.14 (1H, m), 2.58, 2.67, 2.77, 3.02 (together 2H, 4dd, J3.3, 16.2; 4.7, 15.3; 7.9, 15.2; 9.4, 16.3Hz), 3.37 and 3.41, 3.45 (together 2H, ABq, s, J14.7Hz), 3.69-3.95 (2H, m), 4.16-4.36 (1H, m), 4.58 (2H, 30 s), 4.99, 5.00 (together 1H, 2d, J4.8, 4.7Hz), 5.57 (1H, dd, J4.8, 8.8Hz), 6.93-7.07 (3H, m) 7.28-7.36 (2H, m), 7.45, 7.56 (together 1H, 2d, J8.8Hz).

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(d) t-Butyl (RS)-2-Hydroxy-2-[(3R,4R)-3-phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]acetate

5 The azetidinone prepared in Example 1(c), (2.37g) in dichloromethane (10mls) was treated successively with 0.5M t-butyl glyoxylate in 1,2-dichloroethane, (13ml) and triethylamine (87 μ l). The reaction was monitored by t.l.c. analysis (ethyl acetate) until no more starting material remained. The solution was concentrated to a small volume and flash chromatographed on silica gel, eluting with 80% ethyl acetate in hexane. The title compound was obtained as a colourless foam as a mixture of diastereoisomers, (2.65g, 83%); ν_{max} (CH₂Cl₂) 3492, 3405, 1782, 1735 and 1696cm⁻¹; 15 δ_{H} (CDCl₃) 1.38-1.50 (1H, m), 1.54 (9H, s), 1.83-1.95 (2H, m), 2.01-2.10 (1H, m), 2.56-2.89 (2H, m), 3.48-3.64 (2H, m), 3.68-3.80 (1H, m), 3.82-3.92 (1H, m), 4.13-4.24 (1H, m), 4.49-4.55 (1H, m), 4.59 (2H, s), 5.03-5.13 (1H, m), 5.26-5.58 (2H, m), 6.94-7.07 (3H, m), 7.30-7.46 (2H, m) and 20 7.48, 7.44, 7.54, 7.65 (together 1H, 4d, J8.8Hz).

(e) t-Butyl 2-[(3R,4R)-3-Phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]-2-tri-n-butylphosphoranylideneacetate

25 t-Butyl 2-hydroxy-2-[(3R,4R)-3-phenoxyacetamido-4-[2-oxo-3-[(RS)-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]acetate, (2.622g) in dry THF (10ml) was cooled to -20°C under argon. Lutidine (0.828g, 0.898ml) was added followed 30 by the dropwise addition of a solution of thionyl chloride (0.921g, 0.557ml) in THF (5ml). A white precipitate was formed which slowly changed to yellow on warming to 0°C. T.l.c. analysis (ethyl acetate) showed loss of starting material. The reaction mixture was filtered and the solid 35 washed with THF. The solvent was removed from the filtrate.

-35-

and the residue dissolved in toluene. Re-evaporation gave the crude chloride as a brown gum. This was taken up in dioxan (20ml, dried by eluting through alumina), and treated with tri-n-butylphosphine (2.29g, 2.82ml) at ambient temperature for 0.25h. T.l.c. analysis showed formation of product, the solution was diluted with ethyl acetate and washed with water (3x), brine and then dried. Removal of solvent followed by flash chromatography of the residue gave the title compound as a brown gum, (1.726g, 48%);
10 ν_{max} (CH₂Cl₂) 3412, 1764, 1690, 1627 and 1601cm⁻¹; [mass spectrum: +ve ion (thioglycerol) M^+ (693)].

(f) t-Butyl (6R,7R)-7-Phenoxyacetamido-3-[(RS) -tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

15 t-Butyl 2-[3R, 4R-3-phenoxyacetamido-4-[2-oxo-3-[(RS))-tetrahydrofuran-2-yl]prop-1-ylthio]azetidin-2-on-1-yl]-2-tri-n-butylphosphoranylidene acetate, (1.726g) in dry toluene (40 ml) was heated under reflux, under argon
20 overnight. T.l.c. analysis showed loss of starting material with formation of a less polar product. The solution was concentrated and flash chromatographed to give a diastereoisomeric mixture of the title compound as a crisp, pale yellow foam, (0.9g, 76%); ν_{max} (CH₂Cl₂) 3406, 1782, 1714
25 and 1697cm⁻¹; δ_{H} (CDCl₃) 1.54 (10H, s, overlapping m), 1.82-2.17 (3H, m), 2.13, 2.52 (together 1H, 2dd, J9.4, 13.4; 7.0, 13.7Hz), 2.82, 3.04 (together 1H, 2dd, J2.7, 13.3; 4.5, 13.8Hz), 3.41 and 3.63, 3.48 and 3.74 (together 2H, 2ABq, J18.3, 18.1Hz), 3.70-4.17 (3H, m), 4.56, 4.67 (together 1H, 30 2s), 5.00, 5.03 (together 1H, 2d, J5.1, 4.9Hz), 5.85, 5.89 (together 1H, 2dd, J4.8, 9.1; 4.8, 8.8Hz), 6.92-7.70 (3H, m) and 7.26-7.37 (3H, m). [Mass spectrum: +ve ion (3-nitrobenzyl alcohol, sodium acetate) MNa^+ (497)].

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(g) t-Butyl (6R, 7R)-7-Amino-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

t-Butyl (6R, 7R)-7-phenoxyacetamido-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate, (0.87g) in dry dichloromethane (5ml), was cooled to -20°C under argon. N-methylmorpholine (0.408g, 0.443ml) was added followed by a solution of phosphorus pentachloride (0.497g) in dry dichloromethane (12.4ml). The solution was stirred at -20°C for 30 mins and then methanol (5ml) was added in one portion. The solution was allowed to warm to ambient temperature over 1h, and then water (5ml) was added. The reaction was then vigorously stirred for a further 30 minutes. The dichloromethane was removed in vacuo and the residue diluted with ethyl acetate. The pH was adjusted to 7 with 0.880 ammonia. The organic phase was washed with water, brine and dried. Removal of solvent and flash chromatography afforded the title compound as a mixture of diastereoisomers, as a yellow gum, (0.443g, 71%); (Found: 20 M⁺, 340.1461. C₁₆H₂₄N₂O₄S requires M, 340.1457); v_{max}(CH₂Cl₂) 3409(w), 1775 and 1716cm⁻¹; δ_H(CDCl₃) 1.53 (10H, s overlapping m), 1.80-2.14 (3H, m), 2.37, 2.52 (together 1H, 2dd, J9.0, 13.3; 6.8, 13.7Hz), 2.74, 2.99 (together 1H, 2dd, J3.0, 13.5; 4.8, 13.8Hz), 3.38-4.24 (5H, 25 m), 4.70 (1H, d, J4.9Hz), 4.94, 4.96 (together 1H, 2d, J5.1, 5.0Hz).

(h) t-Butyl (6R, 7R)-7-[2-(Z)-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]ceph-3-em-4-carboxylate

2-(Z)-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid hydrochloride (0.664g), as a suspension in dry DMF (4ml), under argon was cooled to -50°C and treated with 35 N,N-diisopropylethylamine (0.357g, 0.481ml) followed by methanesulphonyl chloride, (0.159g, 0.107ml). After 1h at

-37-

-50°C the homogeneous solution was treated with the amino cephalosporin from (g), (0.428g) and pyridine (0.099g, 0.101ml) in DMF (5ml). The reaction mixture was allowed to warm to ambient temperature over 1h, and then diluted with 5 ethyl acetate, washed with water and brine and dried. The solvent was removed in vacuo and the residue flash chromatographed to give a diastereoisomeric mixture of the title compound as a pale yellow foam, (0.727g, 76%)
ν_{max} (CH₂Cl₂) 3397, 1782, 1718 and 1686cm⁻¹; δ_H(CDCl₃), 1.52
10 (10H, s overlapping m), 1.80-2.16 (3H, m), 2.33, 2.51
(together 1H, 2dd, J9.3, 13.3; 7.0, 13.7Hz), 2.80, 3.04
(together 1H, 2dd, J2.7, 13.4; 4.5, 13.7Hz), 3.37-3.89 (5H,
m), 4.05 (3H, s), 5.02, 5.04 (together 1H, 2d, J4.9, 4.6Hz),
5.87 (1H, m) 6.74 (1H, s), 6.87 (1H, d, J8.7Hz,
15 exchangeable), 7.04 (1H, s, exchangeable) and 7.31 (15H, s).
[Mass spectrum: +ve ion (3-Nitrobenzyl alcohol, sodium
acetate) MNa⁺ (788)].

(i) Sodium (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-
20 methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-
ylmethyl]ceph-3-em-4-carboxylate

t-Butyl (6R,7R)-7-[2-(Z)-methoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-[(RS)-tetrahydrofuran-2-yl-
25 methyl]ceph-3-em-4-carboxylate, (0.677g) was dissolved in 0.1M hydrochloric acid in 90% formic acid (8.9ml). After 1h at ambient temperature, concentrated hydrochloric acid, (0.2ml) was added and the reaction continued for a further 0.5h. The white precipitate was filtered off and washed 30 with a little formic acid. The formic acid was removed in vacuo from the filtrate to give a colourless, solid residue. Water (5ml) was added and the pH adjusted to 7 with sodium bicarbonate solution. The slightly turbid solution was eluted through a column of HP20SS, with 1,2,4,6 and 8% THF 35 in water. The fractions containing the title compound, (by h.p.l.c. analysis) were combined, concentrated and

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freeze-dried to give a colourless solid, (0.346g, 80%);
 ν_{max} (KBr) 1757, 1670, 1597 and 1532cm⁻¹; δ_{H} [(CD₃)₂SO]
1.40-1.59 (1H, m), 1.64-1.88 (3H, m), 2.20-2.34 (1H, m),
2.67, 3.04 (together 1H, 2dd, J4.4, 13.0; 6.8, 13.2Hz),
5 3.12-3.60 (3H, m,), 3.68-4.02 (5H, m overlapping s at 3.83),
4.94, 4.96 (together 1H, 2d, J4.6Hz), 5.49 (1H, dd, J4.7,
8.1Hz), 6.74 (1H, s), 7.26 (2H, s, exchangeable) and 9.50
(1H, d, J8.1Hz, exchangeable). [Mass spectrum: +ve ion
(thioglycerol) $\underline{\text{M}}\text{H}^+$ (490)].

10

Example 2

Pivaloyloxymethyl (6R,7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-
methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-
15 ylmethyl] ceph-3-em-4-carboxylate

Pivaloyloxymethyl bromide (0.176g) in acetone (3ml) and sodium iodide (0.135g), under argon were reacted together at room temperature for 0.5h. The acetone was evaporated and 20 replaced with N-methylpyrrolidinone (3ml). This suspension was added to a suspension of sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl] ceph-3-em-4-carboxylate (0.2g) in N-methylpyrrolidinone (3ml). After 1h the solution was 25 diluted with ethyl acetate, washed with water, brine and then dried. After removal of solvent, flash chromatography on silica gel eluting with ethyl acetate, afforded the title compound as a pale yellow foam (0.086g, 36%); ν_{max} (CH₂Cl₂) 3480, 3391, 1786, 1750, 1687 and 1607cm⁻¹; δ_{H} (CDCl₃) 1.24 30 and 1.25 (9H, 2s), 1.43-2.18 (4H, m's), 2.32 and 2.34 (1H, 2dd's, J 9.3, 13.3 and 7.5, 13.7Hz), 2.87 and 3.13 (1H, 2dd's, J 2.5, 13.3 and 3.8, 13.7Hz), 3.47-4.17 (8H, m's overlapping s, 4.12), 5.05 and 5.09 (1H, 2d's, J 4.7 and 4.7Hz), 5.85-5.97 (3H, m), 6.33 (1H, br. s), 7.02 and 7.03 35 (1H, 2s's), 7.48 and 7.55 (1H, 2d's, J 8.7 and 8.8Hz). [Mass spectrum: +ve ion (3NOBA, Na⁺) $\underline{\text{M}}\text{H}^+$ (582), $\underline{\text{M}}\text{Na}^+$ (604)].

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In Vitro Biological Data

MIC (μ g/ml)

Organism

E. coli (NCTC 10418) S. Aureus (Oxford)

5

Example 1	1.0	2.0
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In Vivo Biological Data

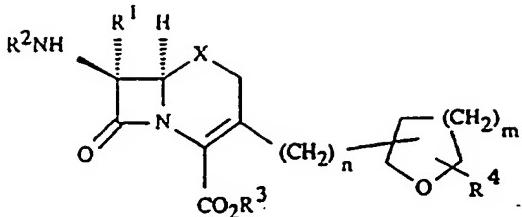
10 Peak serum concentration of the compound from Example 1 was 33.0 μ g/ml, obtained at 30 minutes following oral dosing of the compound from Example 2 to mice at a dose equivalent to 50 mg/kg.

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Claims

1. A compound of formula (I) or a salt thereof:

5



10

wherein

R¹ is hydrogen, methoxy or formamido;

R² is an acyl group;

CO₂R³ is a carboxy group or a carboxylate anion, or R³ is a
15 readily removable carboxy protecting group;

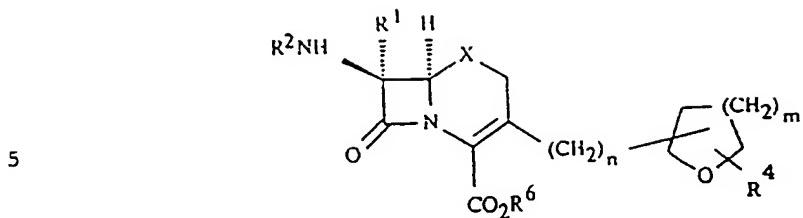
R⁴ represents up to four substituents selected from alkyl,
alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino,
alkylamino, acylamino, dialkylamino, CO₂R, CONR₂, SO₂NR₂
(where R is hydrogen or C₁₋₆ alkyl), aryl and heterocyclyl,
20 which may be the same or different and wherein any R⁴ alkyl
substituent is optionally substituted by any other R⁴
substituent; X is S, SO, SO₂, O or CH₂; m is 1 or 2; and n
is 1, subject to the proviso that when R¹ is hydrogen, X is
S and the 3-position substituent is unsubstituted

25 tetrahydropyran-2-ylmethyl (m=2), then, when R³ is hydrogen,
R² is not 2-thienylacetyl or D- α -aminophenylacetyl, and
when R³ is t-butyl, R² is not 2-thienylacetyl,
D- α -aminophenylacetyl or N-t-butoxycarbonyl-D- α -amino-
phenylacetyl.

30

2. A compound as defined in claim 1 having the formula
(Ia):

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(Ia)

wherein R¹, R², R⁴, m, n and X are as defined with respect
10 to formula (I) in claim 1 and the group CO₂R⁶ is CO₂R³
where CO₂R³ is a carboxy group or a carboxylate anion, or
a pharmaceutically acceptable salt or in vivo hydrolysable
ester thereof, other than 3-(2-tetrahydropyranylimethyl)-7-
(2-thienylacetamido)-3-cephem-4-carboxylic acid or 3-
15 tetrahydropyranylimethyl)-7β-(D-α-phenylglycyl)aminoceph-3-
em-4-carboxylic acid.

3. An in vivo hydrolysable ester of a compound of formula
(Ia) as defined in claim 2.

20

4. A compound of formula (Ia) or a pharmaceutically
acceptable salt or in vivo hydrolysable ester thereof, as
defined in claim 2, other than 3-(2-tetrahydropyranyl-
methyl)-7-(2-thienylacetamido)-3-cephem-4-carboxylic acid or
25 3-(2-tetrahydropyranylimethyl)-7β-(D-α-phenylglycyl)amino-
ceph-3-em-4-carboxylic acid, for use as a therapeutic agent.

5. An in vivo hydrolysable ester of a compound of formula
(Ia) as defined in claim 3 for use in the oral treatment of
30 bacterial infections.

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6. A pharmaceutical composition comprising a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as claimed in claim 2, and a pharmaceutically acceptable carrier.

5

7. An orally administrable pharmaceutical composition comprising an in vivo hydrolysable ester of a compound of formula (Ia), as defined in claim 3, and a pharmaceutically acceptable carrier.

10

8. A method of treating bacterial infections in humans and animals comprising orally administering a therapeutically effective amount of an in vivo hydrolysable ester of a compound of formula (Ia) as defined in claim 3.

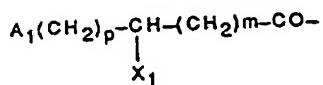
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9. The use of an in vivo hydrolysable ester of a compound of formula (Ia), as defined in claim 3, for the manufacture of a medicament for the oral treatment of bacterial infections.

20

10. A compound as claimed in claim 1, 2 or 3 wherein R¹ is hydrogen.

11. A compound as claimed in claim 1, 2 or 3 wherein R² is 25 an acyl group of formula (a) to (f):



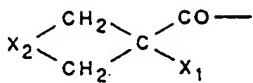
(a)



(b)

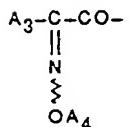
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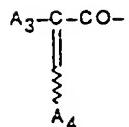
(c)

10



(d)

15



(e)

(f)

wherein p is 0, 1 or 2; m is 0, 1 or 2; A₁ is C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₆ cycloalkyl, cyclohexenyl, cyclohexadienyl, an aromatic or heteroaromatic group; X₁ is 20 a hydrogen or halogen atom, a carboxylic acid, carboxylic ester, sulphonic acid, azido, tetrazolyl, hydroxy, acyloxy, amino, ureido, acylamino, heterocyclylamino, guanidino or acylureido group; A₂ is an aromatic or heteroaromatic group, a substituted alkyl group; or a substituted dithietane; X₂ 25 is a -CH₂OCH₂-, -CH₂SCH₂- or alkylene group; X₃ is an oxygen or sulphur atom; A₃ is an aryl or heteroaryl group; and A₄ is hydrogen, C₁₋₆alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyl(C₁₋₆) alkyl, C₂₋₆ alkenyl, carboxy(C₁₋₆)alkyl, C₂₋₆ alkynyl, aryl or C₁₋₆alkyl 30 substituted by up to three aryl groups.

12. A compound as claimed in claim 11 wherein A₁ is optionally substituted phenyl, X₁ is hydrogen or amino, A₂ is optionally substituted phenyl, X₃ is oxygen, A₃ is

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aminothiazolyl, aminothiadiazolyl or furyl, and A₄ is hydrogen, C₁₋₆ alkyl, or carboxy C₁₋₆ alkyl.

13. A compound as claimed in any one of claims 3, 10, 11
5 or 12 wherein R³ is pivaloyloxymethyl.

14. A compound as claimed in any one of claims 3 and 10 to
13 wherein the cyclic ether group bonded to the 3-position
of the cephalosporin nucleus is unsubstituted or substituted
10 by up to three substituents selected from C₁₋₆ alkyl, C₁₋₆
alkoxy, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkanoyloxy C₁₋₆ alkyl or
C₁₋₆ alkoxy C₁₋₆ alkyl.

15. A compound as claimed in any one of claims 1 to 3 and
15 10 to 14 wherein m is 1.

16. A compound as claimed in any one of claims 1 to 3 and
10 to 14 wherein the cyclic ether group is a
tetrahydrofuran-2-yl or a tetrahydropyran-2-yl group.

20

17. Sodium (6R, 7R)-7-[2-(2-Aminothiazol-4-yl)-2-(Z)-
methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-2-ylmethyl]-
ceph-3-em-4-carboxylate.

25 18. Pivaloyloxymethyl (6R, 7R)-7-[2-(2-Aminothiazol-4-
yl)-2-(Z)-methoxyiminoacetamido]-3-[(RS)-tetrahydrofuran-
2-ylmethyl]ceph-3-em-4-carboxylate.

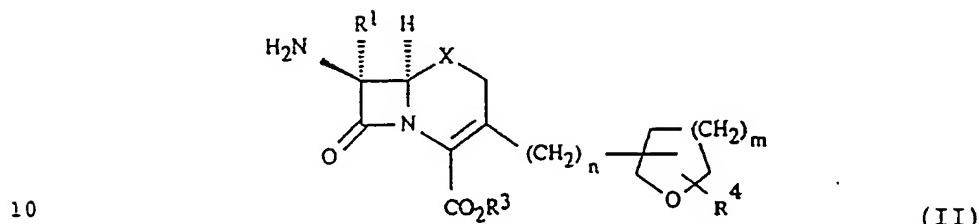
19. A compound of formula (I) as defined in claim 1
30 substantially as hereinbefore described with reference to
the preparative examples.

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20. A process for the preparation of a compound of formula (I) as defined in claim 1 which process comprises:

(a) treating a compound of formula (II) or a salt thereof:

5



wherein R¹, CO₂R³, R⁴, m, n, and X are as hereinbefore defined with respect to formula (I) in claim 1, wherein any reactive group may be protected, and wherein the amino group 15 is optionally substituted with a group which permits acylation to take place, with an N-acylating derivative of an acid of formula (III):

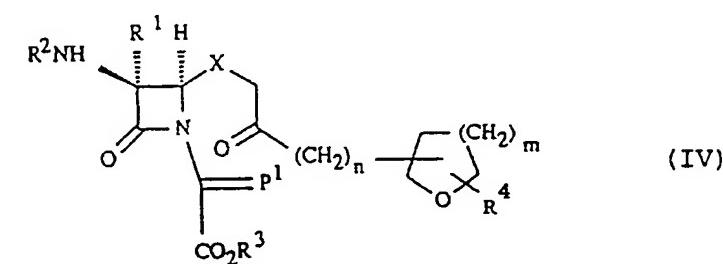
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wherein R^2 is as hereinbefore defined with respect to formula (I) in claim 1 and wherein any reactive group may be protected; or

25

(b) cyclising a compound of formula (IV):

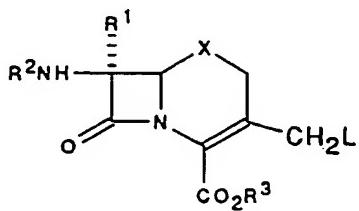


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wherein X, R¹, R², R⁴, m, n and CO₂R³ are as hereinbefore defined with respect to formula (I) in claim 1 and P' is a phosphorus residue; or

5 (c) treating a compound of formula (X):

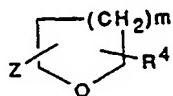
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(X)

wherein R¹, R², CO₂R³ and X are as hereinbefore defined with respect to formula (I) in claim 1, and L is a leaving group, 15 with a compound of formula (XI):

20



(XI)

25

wherein Z is an organo-cuprate group and R⁴ and m are as hereinbefore defined with respect to formula (I) in claim 1;

and thereafter, if necessary or desired, carrying out one of the following steps:

30

i) removing any protecting groups;

ii) converting the group CO₂R³ to a different group CO₂R'³;

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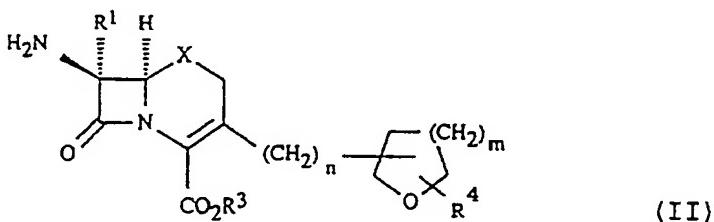
- iii) converting the group R^2 to a different group R^2 ;
- iv) converting the group X to a different group X;
- 5 v) converting the product into a salt.

21. A process for the preparation of a compound of formula (I) substantially as hereinbefore described in the preparative Examples.

10

22. A compound of formula (II) or a salt thereof:

15



20 wherein R^1 , CO_2R^3 , R^4 , X, m and n are as hereinbefore defined with respect to formula (I) in claim 1.

23. t-Butyl 6R,7R-7-Amino-3-(tetrahydrofuran-2-ylmethyl)-ceph-3-em-4-carboxylate.

25

24. A compound of formula (II) as defined in claim 22 substantially as hereinbefore described with reference to the preparative Examples.

30 25. A pharmaceutical composition as claimed in claim 6 or 7 further comprising a β -lactamase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 91/01227

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
 Int.C1.5 C 07 D 501/20 C 07 D 501/18 A 61 K 31/545
 C 07 D 463/00 C 07 D 498/053

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1.5	C 07 D 501/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	FR,A,2166356 (BEEHAM GROUP LTD) 17 August 1973, see pages 51-53; example 7 ---	1-25
A	EP,A,0359536 (BEECHAM GROUP PLC) 21 March 1990, see pages 23-31; claims ---	1-25
A	FR,A,2166355 (BEECHAM GROUP LTD) 17 August 1973, see pages 51-53; example 7, & GB1405758, (cited in the application) ---	1-25

* Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

08-10-1991

Date of Mailing of this International Search Report

04.11.91

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

O. Tobić Nuria TCRIBIC

III. DOCUMENTS CONSIDERED TO BE RELEVANT		(CONTINUED FROM THE SECOND SHEET)
Category ²	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Journal of Medicinal Chemistry,, vol. 20, no. 8, August 1977, American Chemical Society, (Washington, US), Edward G. Brain et al.: "Structure-activity relationships in cephalosporins prepared from penicillins. 2. Analogues of cephalexin substituted in the 3-methyl group", pages 1086-1090, see page 1088, table IV, compounds 35,36, (cited in the application) -----	1-25

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

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V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹ (partially)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim numbers 1-25 because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

The search has been systematically performed for the compounds of formula I and II as far as X represents S and its oxides (the only examples described)

3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9101227
SA 49540

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 24/10/91.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A- 2166356	17-08-73	GB-A-	1405757	10-09-75
		AT-B-	333948	27-12-76
		AU-A-	4856472	09-05-74
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		DE-A-	2254644	19-07-73
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